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Polycavernoside A: The Prins Macrocyclization Approach

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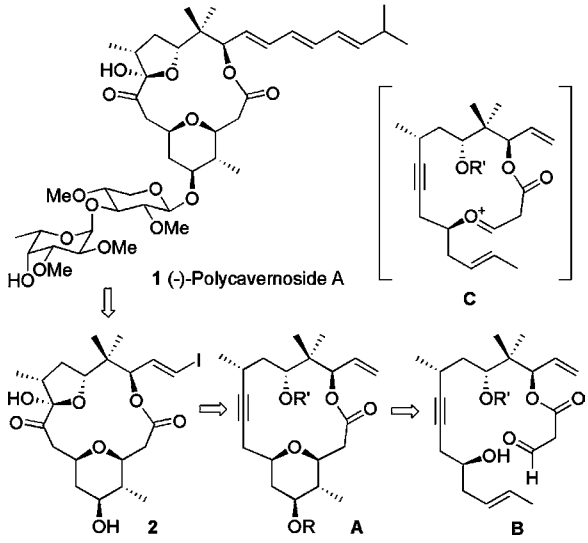
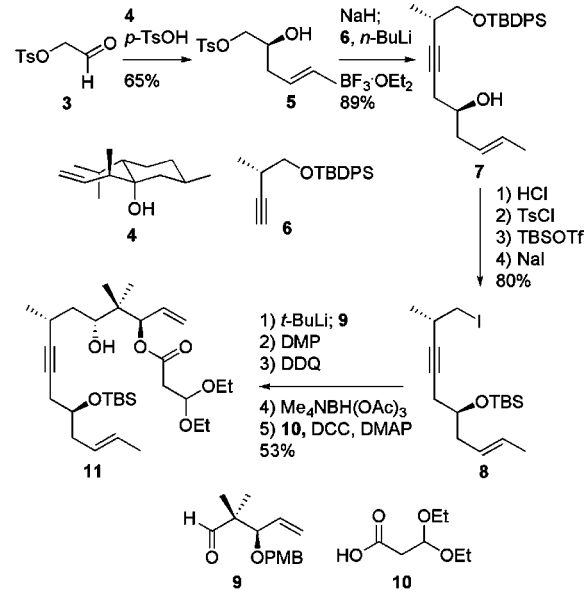
Polycavernoside A (**1**) was isolated by Yasumoto from the edible red alga *Polycavernosa tsudai* as a causative toxin of sudden human intoxication in Guam in 1991.[1] The proposed macrolactone disaccharide structure was confirmed via the first total synthesis by Murai, which also established the absolute stereochemistry.[2] In the Murai synthesis, Yamaguchi lactonization of the hydroxycarboxylic acid precursor containing a preformed oxane subunit yielded a key macrolide intermediate. Similar strategies were also adopted in the later syntheses by Paquette[3] and White.[4,5] We were intrigued by the possibility of using an intramolecular Prins macrocyclization protocol[6−8] in the synthesis of **1**. Aldehydo homoallylic alcohol **B** may undergo a Prins cyclization reaction to produce macrolactone **A**, from which the known macrolactone intermediate **2** may be prepared. The success of this macrobicyclization reaction would hinge on the viability of the macrocyclic oxocarbenium ion **C** (Scheme 1).

Scheme 1. Retrosynthetic Analysis



In practice, the reaction of hydroxyacetaldehyde tosylate (**3**) with the Nokami alcohol **4**[9] under acidic conditions produced homoallylic alcohol **5**. The epoxide generated from **5** was reacted with the known alkyne **6**[10] after lithiation, and enynol **7** was prepared smoothly. TBDPS deprotection, regioselective tosylation, TBS protection of the secondary hydroxyl group, and iodide substitution produced primary iodide **8** without difficulty. Lithium−halogen exchange and reaction with the known aldehyde **9**[4b] led to the formation of secondary alcohol products (1:1.4), which were converted into the corresponding ketone. DDQ deprotection of the PMB group and reduction with tetramethylammonium triacetoxyborohydride led to the predominantly (6:1) anti diol product, which was condensed with carboxylic acid **10** to produce ester **11** (Scheme 2).

Scheme 2. Preparation of the Acyclic Ester Intermediate



Acetate protection of the secondary hydroxyl group in **11** and TBS deprotection led to acetal homoallylic alcohol **12**. The crucial Prins macrocyclization reaction of **12** proceeded smoothly in the presence of TES triflate, TMS acetate, and acetic acid[6] to produce an 85% yield of a product mixture containing mainly (6:1) the desired macrolactone **13** (Scheme 3). The minor product was the acetoxy epimer. Treatment of **13** with excess ozone led to diketone aldehyde **14** as expected. Problems arose when **14** was subjected to the Takai conditions;[11] only a complex product mixture was obtained, and it was not possible to obtain the desired iodoolefin.

The diketone functionality obviously interfered under the Takai conditions. Selective protection of the aldehyde or diketone group appeared to be impractical, and acetate removal was also sluggish. It was then decided to employ diol intermediate **15** in the Prins macrocyclization step; this diol can be prepared from **11** via TBS deprotection. The rationale was that the extra hydroxyl group would not participate in the formation of a cyclic oxocarbenium ion that is also an eight-membered heptanolactone. In practice, acetal diol **15** underwent Prins macrocyclization smoothly under the usual conditions, producing mainly (5.5:1) macrolactone **16** (Scheme 4).

The intramolecular alkyne hydration reaction proceeded predominantly in the 6-endo mode, mainly producing cyclic enol ether **17** from alkynol **16** in the presence of a platinum(II) catalyst.[12] Oxidation of **17** with dimethyldioxirane and addition of methanol led to a hydroxy ketal intermediate, which was converted into keto ketal **18** under Ley oxidation conditions.[13] The corresponding aldehyde was prepared via ozonolysis of **18**, which was converted into the corresponding iodoolefin under Takai conditions. Prolonged exposure to the Takai conditions also resulted in the rearrangement

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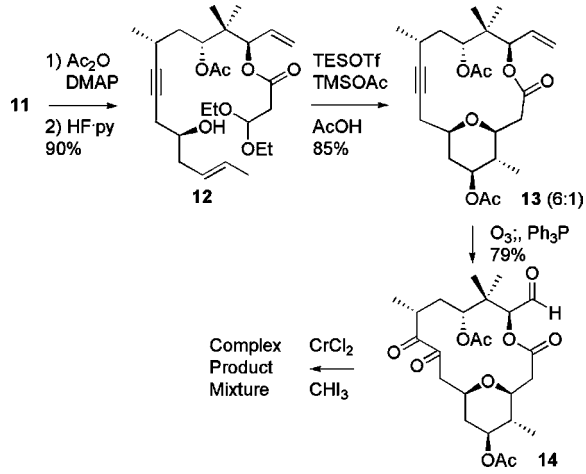
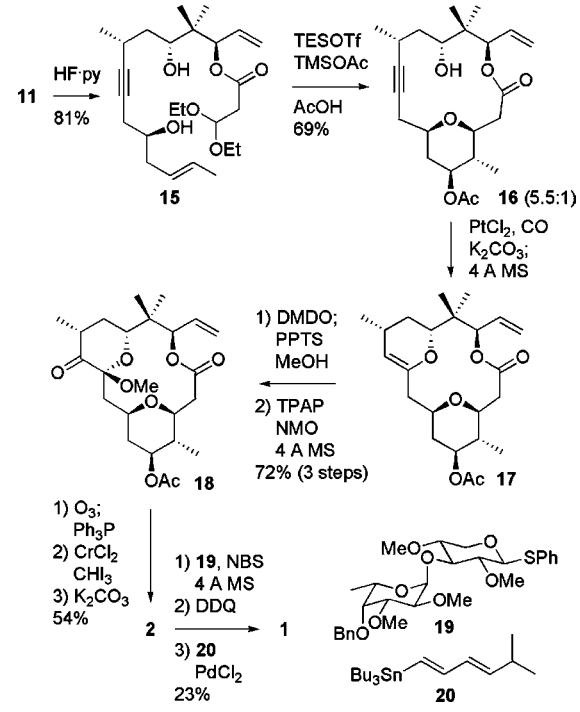
Scheme 3. Prins Cyclization and Preparation of a Diketone Aldehyde Intermediate



Scheme 4. Alternative Prins Cyclization and Synthesis of Polycavernoside A (**1**)



to the five-membered-ring hemiacetal. Basic hydrolysis led to the known intermediate **2**. Glycosylation of **2** in the presence of the known glycosyl sufide **19**,[4b] oxidative benzyl deprotection of the benzyl ether group with DDQ, and a Stille-type coupling reaction with the known dienylstannane **20**[3b] led to (−)-polycavernoside A (**1**).

The present scheme represents a facile route to polycavernoside A (**1**). In particular, the key bicyclic macrolactone **16** was prepared directly from an acyclic precursor, **15**. Future studies will focus on further applications of the Prins macrocyclization strategy in the synthesis of complex natural products.

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Supporting Information Available: Selected experimental procedures and ^{1}H and ^{13}C NMR spectra of selected intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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